

## **REMARKS**

### **I. INTRODUCTION**

Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

Claims 1, 19, 36 and 44 are currently being amended.

Claims 52-55 are being added.

This amendment adds, changes and/or deletes claims in this application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier.

After amending the claims as set forth above, claims 1, 15, 19, 24, 28-39, 41-47, 49-55 are now pending in this application.

### **II. THE PERSONAL INTERVIEW**

The undersigned appreciates the courtesies extended to her during the personal interview of January 4, 2005. During the interview the Examiner and the undersigned discussed the cited prior art and the undersigned discussed Applicants' position with respect to the limitations in Richter and Levy.

### **III. THE OFFICE ACTION**

#### **Rejection based on 35 U.S.C. § 103**

Claims 1, 15, 19, 24, 28-39, 41-47 and 49-52 have been rejected under 35 U.S.C. § 103 as allegedly unpatentable over the combined teachings of Levy (U.S. Patent No. 5,283,255) and Richter (U.S. Patent No. 5,705,518). Applicants respectfully traverse.

#### **A. The Examiner's Rationale**

The Examiner relies on Levy to teach that photosensitizing agents such as hydromonobenzoporphyrins can be used in photodynamic therapy for the treatment of athlete's foot and fungal diseases in general. However, Levy does not teach the use of 5-aminolevulinic acid (5-ALA), a precursor to protoporphyrin IX. The Examiner relies on

Richter to teach that photosensitizing agents such as the porphyrins provide the same effect as 5-ALA. Therefore, the Examiner concludes that it would have been obvious to use 5-ALA in the method of Levy, which is directed to treating athlete's foot, which is caused by the same fungus as the fungus which causes onychomycosis.

**B. One Skilled in the Art Would Not Consider the Combined Teachings of Levy and Richter to Teach the Claimed Invention**

The Examiner asserts that Levy envisioned treating fungal infections of the skin. Applicants disagree. Rather, Applicants believe that Levy, although briefly mentioning that her photodynamic therapy methodology could be used for treating athlete's foot and fungal infections, fails to teach one skilled in the art how to make and use the hydromonobenzoporphyrins for treating onychomycosis.

Currently, it is well established that onychomycosis is notoriously difficult to treat. See Campbell et al., stating, "[o]nychomycosis is a common nail disease responsible for approximately 50% of disease of the nail . . . the diagnosis and treatments are difficult and the choice of appropriate antifungal drugs complex and require the knowledge of the chemical structures of the metabolites of the molds that cause onychomycosis and their interaction with the antifungal drugs" (Abstract, Scientific World Journal, 2004 Aug 31; 4; 760-777-**Exhibit 1**). See also Gupta et al. stating, "[o]nychomycosis is a fungal infection affecting the nail bed and nail plate; it may be chronic and can be difficult to treat" (Abstract, Am. J. Clin. Dermatol. 2004; 5(4); 225-37-**Exhibit 2**). In addition, Albert et al. recognize the difficulty in treating onychomycosis, where they state, "[o]f all superficial fungal infections, onychomycosis is the most difficult to manage. Practitioners of all disciplines realize its chronic nature, difficulty in eradication and propensity to recur" (Abstract, Clin. Podiatr. Med. Surg. 2004 Oct. 21(4); 605-15-**Exhibit 3**). Omero et al. supports this proposition, "[o]nychomycosis--the dermatophytic invasion of the nail--is difficult to eradicate with drug treatment" (Abstract, Mycopathologia, 2004 Aug; 158(2): 173-80-**Exhibit 4**).

Each of the references above were published after the filing date of the present application (the effective filing date of the present application is June 5, 1995). In fact, all the references are published in 2004. Thus, one skilled in the art at the time of the present

invention would have understood the difficulty in achieving effective treatment of onychomycosis.

Only recently have studies been performed directed to the use of photodynamic therapy for treatment of the dermatophyte *Trichophyton*, one of the fungi which can cause onychomycosis.<sup>1</sup> Smijs et al. disclose using porphyrins for photodynamic killing of the dermatophyte. In fact, Smijs states, “[t]he present study shows that *Trichophyton rubrum* in suspension culture is susceptible to photodynamic treatment, a completely new application in this area.” See *Photochem. Photobiol* 2003 May; 77(5): 556-60, abstract-**Exhibit 5**. In a later publication also by Smijs, he states, “[t]he application to photosensitizers for the treatment of fungal infections is a new and promising development within the field of photodynamic therapy.” See *Photochem. Photobiol* 2004 Sep-Oct; 80(2): 197-202, abstract-**Exhibit 6**.

The Examiner’s interpretation of Levy and Richer to establish that the present invention is *prima facie* obvious over the teachings therein is improper in light of the current knowledge of one skilled in the art. Although the references in Exhibits 1-6 are post-filing references, they establish the level of knowledge of skill in the art to date. Since the level of skill in the art is ever expanding and not contracting, the references establish that at the time of Applicants’ filing (effective filing date, June 5, 1995), no one would have considered treatment of onychomycosis with any type of photodynamic therapy to be within the purview of one skilled in the art.

### **C. The Photosensitizing Agents of Levy Act by a Different Pathophysiology as Compared to the Present Agents**

In addition, the Examiner discussed with the undersigned during the personal interview of January 4, 2005 that the photosensitizing porphyrin agents of Levy, when administered are converted into porphyrins, and it is these porphyrins which are involved in the heme biosynthetic pathway. Contrary to this position, the photosensitizing agent, VISUDYNE®, a vertiporphyrin, is transported in the plasma primarily by lipoproteins and

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<sup>1</sup> The primary fungi that cause onychomycosis are *trichophyton rubrum* and *trichophyton mentagrophytes*. They are dermatophytes (fungi that infect hair, skin, and nails) and feed on keratinized (nail) tissue. The infections they cause are normally confined to the nails, but occasionally spread to the surrounding skin. Another type of onychomycosis is caused by yeast (*candida albicans* or *candida parapsilosis*). These infections are less common but produce similar symptoms. See <http://www.podiatrychannel.com/onychomycosis>

once is it activated by light in the presence of oxygen, highly reactive, short-lived singlet oxygen and reactive oxygen radicals are generated (See Exhibit 7-product insert for VISUDYNE®). It is these radicals which are responsible for the beneficial effects of the photosensitizing agent.

In the present application, an exogenous agent is administered (e.g., 5-ALA), which is not itself a photosensitizing agent, but which induces accumulation of protoporphyrin IX, an endogenous photosensitizer. Levy is directed to compounds, hydromonobenzoporphyrins, primarily used for treating tumor cells (*ex vivo* and *in vivo*), eliminating viral contaminants in a blood sample (*ex vivo*) and treating papilloma-caused warts.

The compounds of Levy are pre-formed photosensitizers which are photoactive before administration, at the time of administration and after administration. Because the compounds in Levy are pre-formed, their uptake, photoactivity, and elimination are completely independent of the heme biosynthetic pathway and independent of the endogenous photosensitizer, protoporphyrin IX.

The presently elected agent for use in the claimed photodynamic methodology is 5-ALA, which, on the other hand, depends on the presence of heme biosynthesis within the cells in order to cause the accumulation of protoporphyrin IX. The heme biosynthetic pathway is an enzymatically controlled metabolic process within cells; it is specific to certain compounds, one of which is 5-ALA, none of which are those in Levy. Since the compounds of Levy act by a different pathophysiology, one skilled in the art would not identify a compound disclosed in Richter, such as 5-ALA, to be an art recognized equivalent for the Levy compounds and therefore would not substitute a compound from Richter for one of the compounds of Levy. The present claims require that the agent administered is not a photosensitizing agent in itself. None of the Levy compounds fall within this definition.

Thus, there is no expectation by one skilled in the art at the time of the invention that 5-ALA and the compounds of Levy would behave in a similar manner. Moreover, in light of the difficulty of achieving effective treatment of onychomycosis, one skilled in the art, armed with both Levy and Richter would not have arrived at the presently elected invention. Therefore, the presently claimed invention is patentable over the combined teachings of Levy and Richter.

#### IV. CONCLUSION

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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